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Smell and Taste: The Chemical Senses

THROUGH THE SENSES OF SMELL and taste we are able to perceive a staggering number and variety of chemicals in the external world. These chemical senses inform us about the availability of foods and their potential pleasure or danger. Smell and taste also initiate physiological changes required for the digestion and utilization of food. In many animals the olfactory system also serves an important social function by detecting pheromones that elicit innate behavioral or physiological responses.

Although the discriminatory ability of humans is somewhat limited compared with that of many other animals, odor chemists estimate that the human olfactory system may be capable of detecting more than 10,000 different volatile chemicals. Perfumers who are highly trained to discriminate odorants can distinguish as many as 5,000 different types of odorants, and wine tasters can discern more than 100 different components of taste based on combinations of flavor and aroma.

In this chapter we consider how odor and taste stimuli are detected and how they are encoded in patterns of neural signals transmitted to the brain. In recent years much has been learned about the mechanisms underlying chemosensation in a variety of animal species. Certain features of chemosensation have

been conserved through evolution, whereas others are specialized adaptations of individual species.

A Large Number of Olfactory Receptor Proteins Initiate the Sense of Smell

Odorants—volatile chemicals that are perceived as odors—are detected by olfactory sensory neurons in the nose. The sensory neurons are embedded in a specialized olfactory epithelium that lines part of nasal cavity, approximately 5 cm^2 in area in humans (Figure 32–1), and are interspersed with glia-like supporting cells (Figure 32–2). They are relatively short-lived, with a life span of only 30 to 60 days, and are continuously replaced from a layer of basal stem cells in the epithelium.

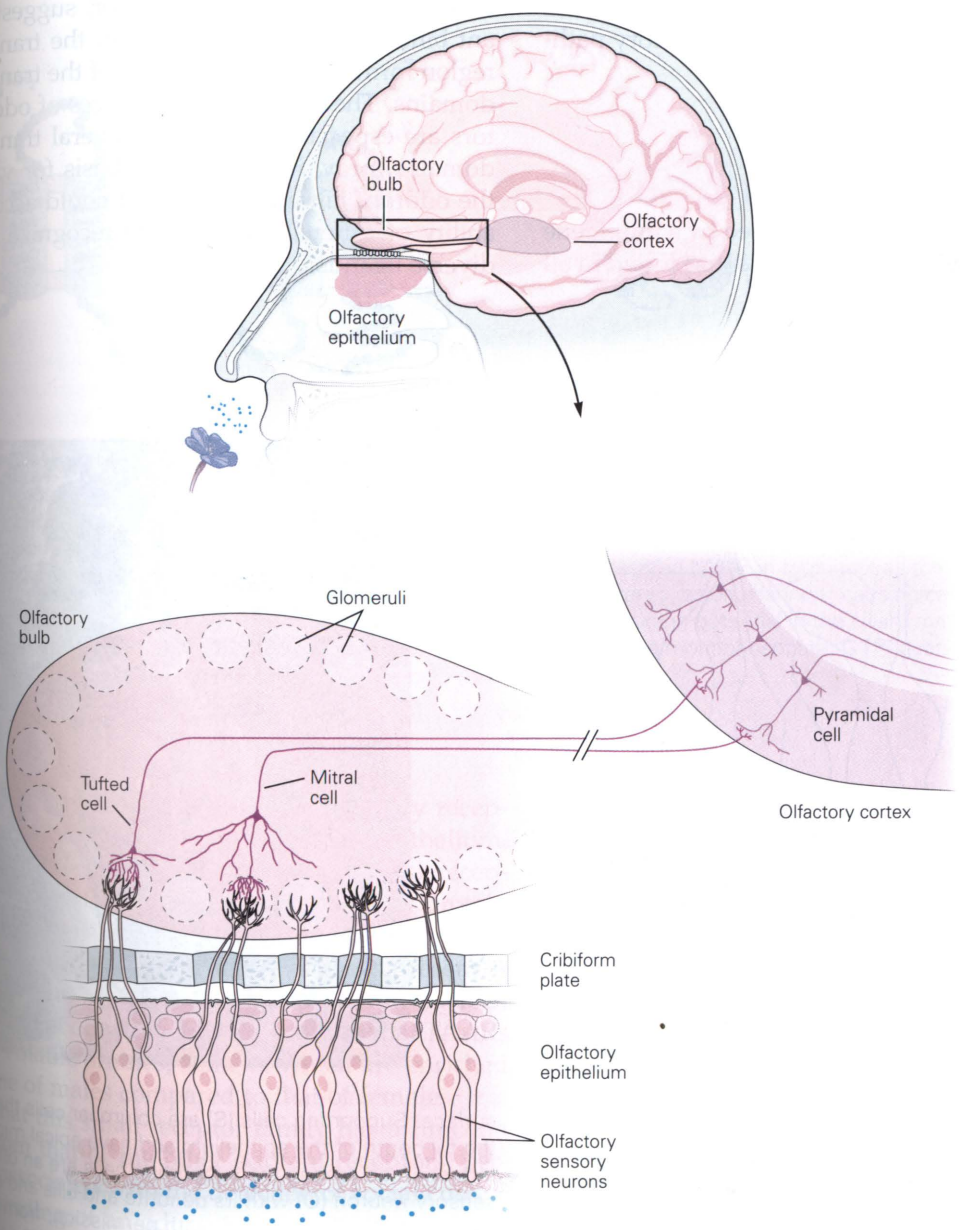


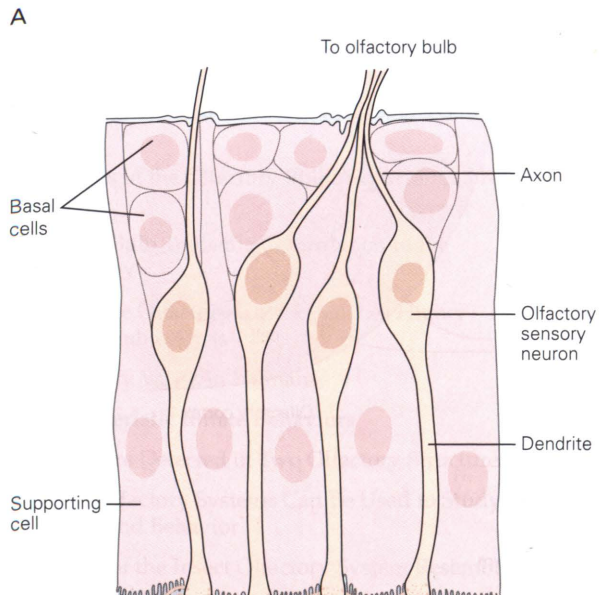
Figure 32–1 The olfactory system. Odorants are detected by olfactory sensory neurons in the olfactory epithelium, which lines part of the nasal cavity. The axons of these neurons project to the olfactory bulb where they terminate on mitral and tufted cell relay neurons within glomeruli. The relay neuron axons project to the olfactory cortex where they terminate on the dendrites of pyramidal neurons whose axons project to other brain areas.

The olfactory sensory neuron is a bipolar nerve cell. A single dendrite extends from the apical end to the epithelial surface, where it gives rise to numerous thin cilia that protrude into the mucus that coats the nasal cavity (Figure 32–2). The cilia have receptors that recognize odorants as well as the transduction machinery needed to amplify the sensory signals and transform them into electrical signals in the neuron's axon, which projects from the basal pole of the neuron to the brain. The axons of olfactory sensory neurons pass through the cribriform plate, a perforated region in the skull above the nasal cavity. The axons then synapse in the olfactory bulb, the first relay in the olfactory pathway (see Figure 32–1).

Mammals Share a Large Family of Odorant Receptors

Odorant receptors are proteins encoded by a multigene family that is evolutionarily conserved and found in all vertebrate species. Humans have approximately 350 different odorant receptors, whereas mice have approximately 1,000. Although odorant receptors belong to the G protein-coupled receptor superfamily, they share sequence motifs not seen in other superfamily members. Significantly, the odorant receptors vary considerably in amino acid sequence (Figure 32–3A).

Like other G protein-coupled receptors, odorant receptors have seven hydrophobic regions that are likely to serve as transmembrane domains (Figure 32–3A). Detailed studies of other G protein-coupled receptors, such as the β-adrenergic receptor, suggest that odorant binding occurs in a pocket in the transmembrane region formed by a combination of the transmembrane domains. The amino acid sequences of odorant receptors are especially variable in several transmembrane domains, providing a possible basis for variability in the odorant binding pocket that could account for the ability of different receptors to recognize structurally diverse ligands.



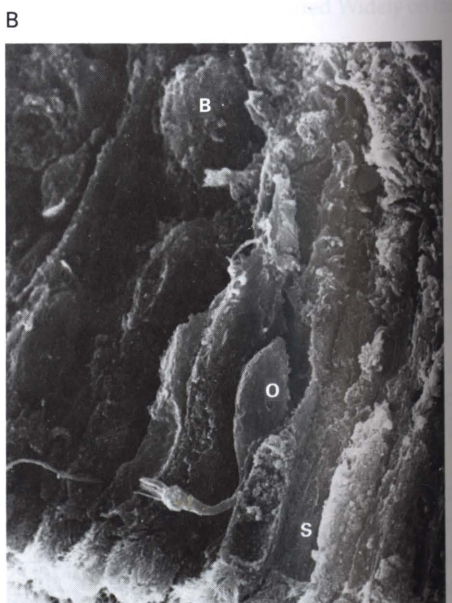


Figure 32–2 The olfactory epithelium.

A. The olfactory epithelium contains sensory neurons interspersed with supporting cells as well as a basal layer of stem cells. Cilia extend from the dendrite of each neuron into the mucus lining the nasal cavity. An axon extends from the basal end of each neuron to the olfactory bulb.

B. A scanning electron micrograph of the olfactory epithelium shows the dense mat of sensory cilia at the epithelial surface. Supporting cells (**S**) are columnar cells that extend the ful depth of the epithelium and have apical microvilli. Interspersed among the supporting cells are an olfactory sensory neuron (**O**) with its dendrite and cilia and a basal stem cell (**B**). (Reproduced, with permission, from Morrison and Costanzo 1990.)

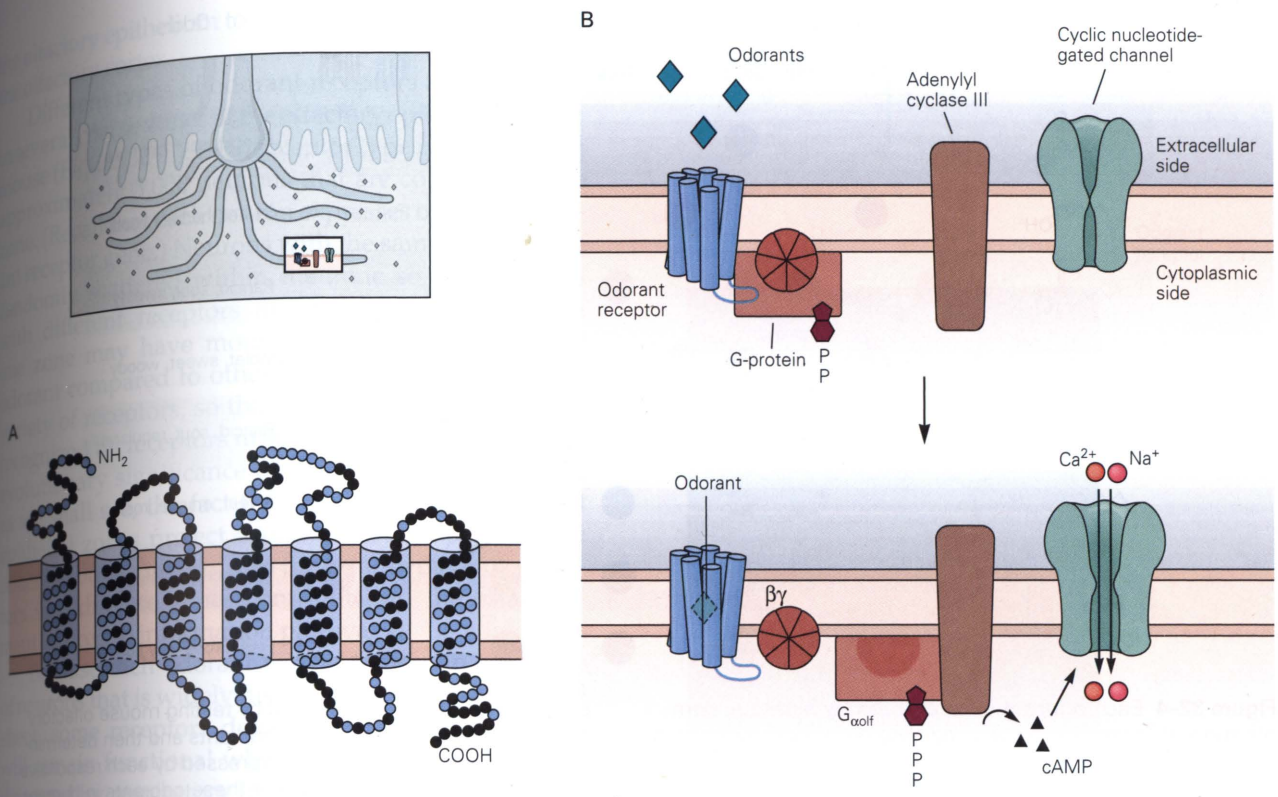


Figure 32–3 Odorant receptors.

A. Odorant receptors have the seven transmembrane domains characteristic of G protein-coupled receptors. They are related to one another but vary in amino acid sequence (positions of highest variability are shown here as **black balls**). Humans have approximately 350 different odorant receptors, and mice have approximately 1,000. (Reproduced, with permission, from Buck and Axel 1991.)

B. Binding of an odorant causes the odorant receptor to interact with $G_{\alpha olf}$, the α-subunit of a heterotrimeric G protein. This causes the release of a GTP-coupled $G_{\alpha olf}$, which stimulates adenylyl cyclase III, leading to an increase in cAMP. The elevated cAMP in turn induces the opening of cyclic nucleotide-gated cation channels, causing cation influx and a change in membrane potential in the ciliary membrane. (**cAMP**, cyclic adenosine monophosphate; **GTP**, guanosine triphosphate.)

A second, smaller family of chemosensory receptors is also expressed in the olfactory epithelium. These receptors, called trace amine-associated receptors (TAARs), are G protein-coupled, but their protein sequence is unrelated to that of odorant receptors. They are encoded by a small family of genes present in humans and mice as well as fish. Studies in mice, which have 14 different olfactory TAARs, indicate that TAARs recognize volatile amines, some of which are enriched in the urine of males compared to that of females. It is possible that this small receptor family has a function distinct from that of the other odorant receptors, perhaps one associated with the detection of social cues.

The binding of an odorant to its receptor induces a cascade of intracellular signaling events that depolarize the olfactory sensory neuron (Figure 32–3B). The depolarization spreads passively to the cell body of the olfactory sensory neuron, causing action potentials that are actively conducted in the axon to the olfactory bulb.

Humans and other animals rapidly accommodate to odors, as witnessed by the weakening of an unpleasant odor when it is continuously present. The ability to sense an odorant rapidly recovers when the odorant is temporarily removed. The adaptation to odorants is caused in part by modulation of the cyclic nucleotide-gated ion channel, but the mechanism by which sensitivity is speedily restored is not yet understood.

Different Combinations of Receptors Encode Different Odorants

To be distinguished perceptually, different odorants must cause different signals to be transmitted from the nose to the brain. This is accomplished in two ways.

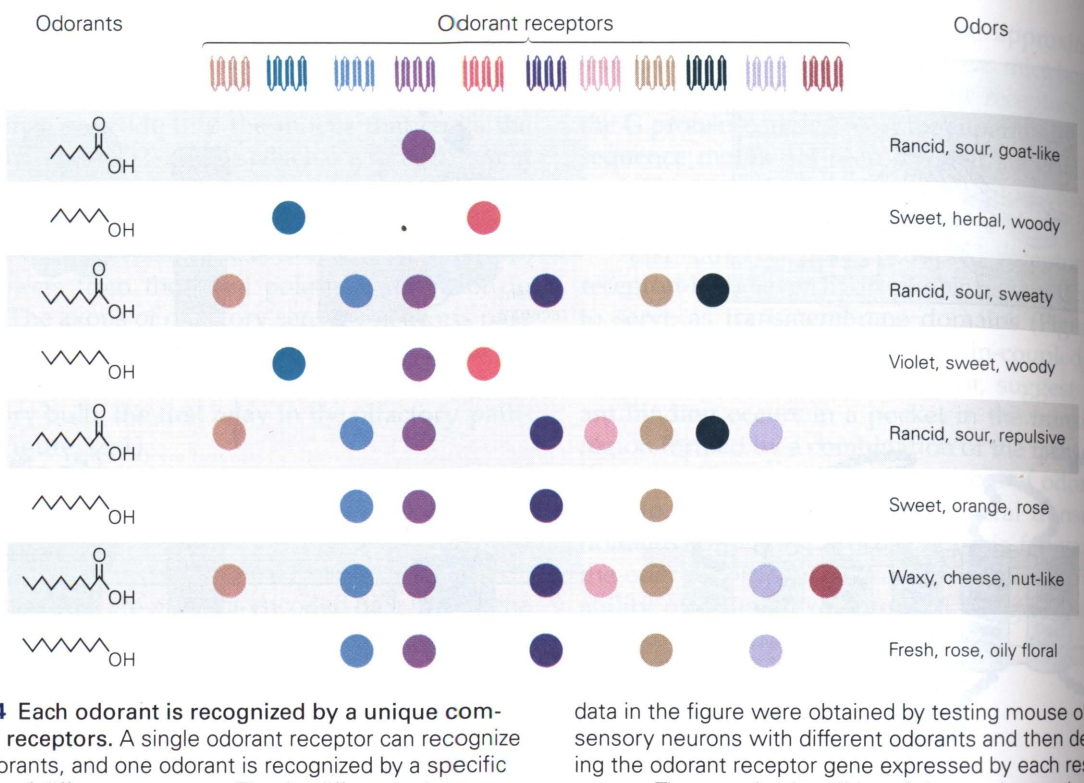


Figure 32–4 Each odorant is recognized by a unique combination of receptors. A single odorant receptor can recognize multiple odorants, and one odorant is recognized by a specific combination of different receptors. That is, different odorants are detected by different combinations of receptors. This combinatorial coding of specific odorants explains how mammals can distinguish odorants with similar chemical structures. The data in the figure were obtained by testing mouse olfactory sensory neurons with different odorants and then determining the odorant receptor gene expressed by each responsive neuron. The perceived qualities of these odorants in humans are shown on the right. (Adapted, with permission, from Malnic et al. 1999.)

First, each olfactory sensory neuron expresses only one odorant receptor gene and therefore one type of receptor. Second, each receptor recognizes multiple odorants, and conversely each odorant is detected by different types of receptors. Importantly, however, each odorant is detected by a unique constellation of receptors and thus causes a distinctive pattern of signals to be transmitted to the brain.

The combinatorial coding of odorants greatly expands the discriminatory power of the olfactory system. If each odorant were detected by only three different receptors, this strategy could in theory generate millions of different receptor combinations—and an equivalently vast number of different signaling patterns. Interestingly, even odorants with nearly identical structures are recognized by different combinations of receptors (Figure 32–4). The fact that highly related odorants have different receptor codes explains why a slight change in the structure of an odorant can alter its perceived odor. In some cases the result is dramatic, for example changing the perception of a chemical from rose to sour.

A change in concentration of an odorant can also change the perceived odor. For example, a low concentration of thio terpineol smells like tropical fruit, a higher concentration smells like grapefruit, and an even higher concentration smells putrid. As the concentration of an odorant is increased, additional receptors with lower affinity for the odorant are recruited into the response and change the receptor code, providing an explanation for the effects of odorant concentration on perception.

Olfactory Information Is Transformed Along the Pathway to the Brain

Odorants Are Encoded in the Nose by Dispersed Neurons

How is a large array of different odorant receptors organized to generate diverse odor perceptions? This question has been investigated in the mouse. Studies in mice have revealed that olfactory information undergoes a series of spatial transformations as it travels from

the olfactory epithelium to the olfactory bulb and then to the olfactory cortex.

Different types of odorant receptors are expressed in several coarse zones of the olfactory epithelium of the mouse (Figure 32–5). Each receptor type is expressed in approximately 5,000 neurons that are confined to one zone. (Recall that each neuron expresses only one odorant receptor gene.) Neurons with the same receptor are randomly scattered within the zone so that neurons with different receptors are interspersed. Although one zone may have more receptors for a particular odorant compared to other zones, all zones contain a variety of receptors, so that a specific odorant may be recognized by receptors in several different zones. The evolutionary significance of the zones is unclear, but, as we shall see, the fact that neurons within different epithelial zones project axons to distinct parts of the olfactory bulb suggests that the arrangement of receptors into discrete zones contributes to the establishment of precise information pathways.

Because each odorant is detected by an ensemble of neurons that is widely dispersed across the epithelial sheet, some receptors detecting a particular odorant will remain functional when part of the epithelium is damaged by respiratory infection.

Sensory Inputs in the Olfactory Bulb Are Arranged by Receptor Type

The axons of olfactory sensory neurons project to the ipsilateral olfactory bulb, whose rostral end lies just above the olfactory epithelium. The sensory axons terminate on the dendrites of olfactory bulb neurons within bundles of neuropil called glomeruli that are arrayed over the bulb's surface (Figure 32–6). In each glomerulus the sensory axons make synaptic connections with three types of neurons: mitral and tufted relay neurons, which project axons to the olfactory cortex, and periglomerular interneurons, which encircle the glomerulus.

The axon of an olfactory sensory neuron terminates in only one glomerulus. Similarly, the primary dendrite of each mitral and tufted relay neuron is confined to a single glomerulus. In each glomerulus the axons of several thousand sensory neurons converge on the dendrites of approximately 40 to 50 relay neurons. This convergence results in approximately a 100-fold decrease in the number of neurons transmitting olfactory signals.

The organization of sensory information in the olfactory bulb is dramatically different from that of the epithelium. Whereas olfactory sensory neurons with the same odorant receptor are randomly

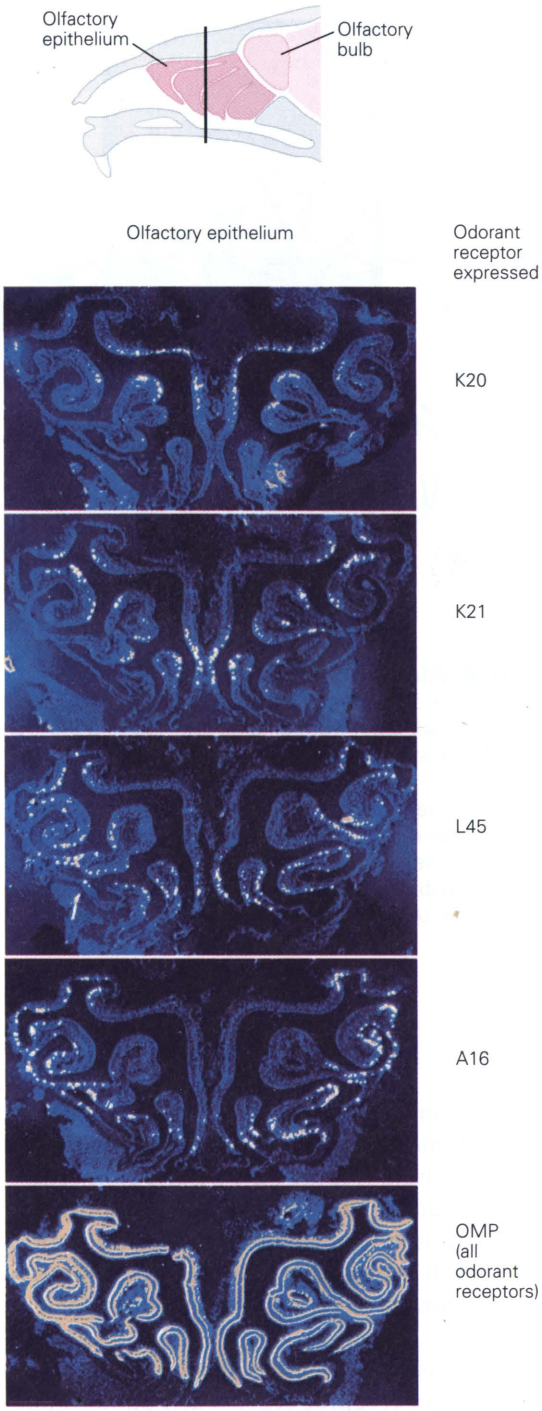


Figure 32–5 Organization of sensory inputs in the olfactory epithelium. Sensory neurons in the olfactory epithelium are distributed in discrete areas known as zones, and each odorant receptor gene is expressed by a small subset of neurons within a single zone. Neurons labeled by four different receptor probes are shown here in different zones in sections through the mouse nose. An olfactory marker protein (OMP) probe labels all neurons expressing odorant receptors. (Adapted, with permission, from Ressler, Sullivan, and Buck 1993; adapted, with permission, from Sullivan et al. 1996.)

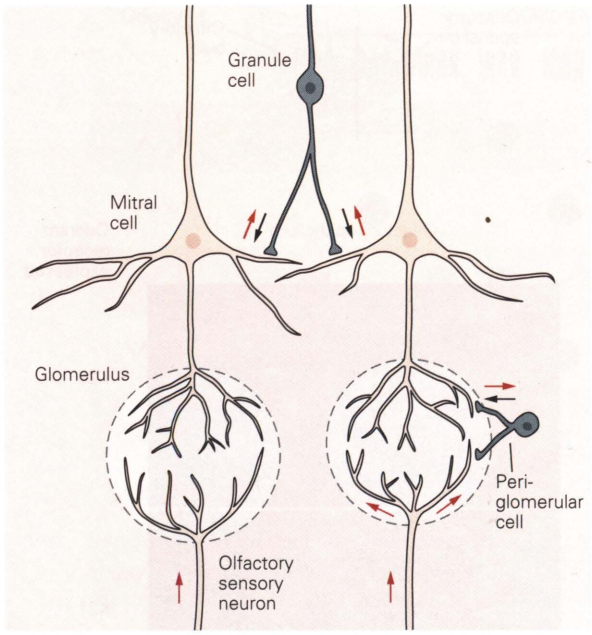


Figure 32–6 Olfactory bulb interneurons. Within the glomerulus, the dendrites of GABAergic periglomerular cells receive excitatory input from olfactory sensory neurons and have reciprocal synapses with the primary dendrites of mitral and tufted relay neurons, suggesting a possible role in signal modification. The dendrites of GABAergic granule cells deeper in the bulb have reciprocal excitatory-inhibitory synapses with the secondary dendrites of the relay neurons and are thought to provide negative feedback to relay neurons that shapes the odor response. (Adapted, with permission, from Shepherd and Greer 1998.)

scattered in one epithelial zone, their axons converge in a few glomeruli at two spots, one on either side of the olfactory bulb (Figure 32–7). Each glomerulus, and each mitral and tufted relay neuron connected to it, receives input from just one type of odorant receptor. The result is a precise arrangement of inputs from different odorant receptors, which is similar between individuals.

Because each odorant is recognized by a unique combination of receptor types, each odorant also activates a particular combination of glomeruli in the olfactory bulb (Figure 32–7B). At the same time, just as an odorant receptor recognizes multiple odorants, a single glomerulus—or a given mitral or tufted cell—is activated by more than one odorant. Closely related odorants can stimulate glomeruli in the same subregion of the bulb, suggesting that the organization of inputs is related to odorant structure. Owing to the nearly stereotyped pattern of receptor inputs in the olfactory bulb, the patterns of glomerular activation elicited by individual odorants are similar in all individuals and are bilaterally symmetrical in the two adjacent bulbs.

This organization of sensory information in the olfactory bulb is likely to be advantageous in two respects. First, the fact that signals from thousands of sensory neurons with the same odorant receptor type always converge on the same few glomeruli and relay neurons in the olfactory bulb may optimize the detection of odorants present at low concentrations. Second, although olfactory sensory neurons with the same receptor type are dispersed and are continually replaced, the arrangement of inputs in the olfactory bulb remains unaltered. As a result, the neural code for an odorant in the brain is maintained over time, assuring that an odorant encountered previously can be recognized years later.

One mystery that remains unsolved is how all the axons of olfactory sensory neurons with the same type of receptor are directed to the same glomeruli. Studies using transgenic mice indicate that the odorant receptor itself somehow determines the target of the axon, but how it does so is unclear.

Sensory information is processed and possibly refined in the olfactory bulb before it is forwarded to the olfactory cortex. Each glomerulus is encircled by periglomerular interneurons that receive excitatory input from sensory axons and form inhibitory dendrodendritic synapses with mitral and tufted cell dendrites in that glomerulus and perhaps adjacent glomeruli. The periglomerular interneurons may therefore have a role in signal modulation. In addition, granule cell interneurons deep in the bulb provide negative feedback onto mitral and tufted cells. The granule cell interneurons are excited by the basal dendrites of mitral and tufted cells and in turn inhibit those postsynaptic relay neurons and others with which they are connected. The lateral inhibition afforded by these connections is thought to dampen signals from glomeruli and relay neurons that respond to an odorant only weakly, thereby sharpening the contrast between important and irrelevant sensory information before its transmission to the cortex.

Other potential sources of signal refinement are the retrograde projections to the olfactory bulb from the olfactory cortex, basal forebrain (horizontal limb of the diagonal band), and midbrain (locus ceruleus and raphe nuclei). These connections may modulate olfactory bulb output according to the physiological state of an animal. When the animal is hungry, for example, some centrifugal projections might heighten the perception of the aroma of foods.

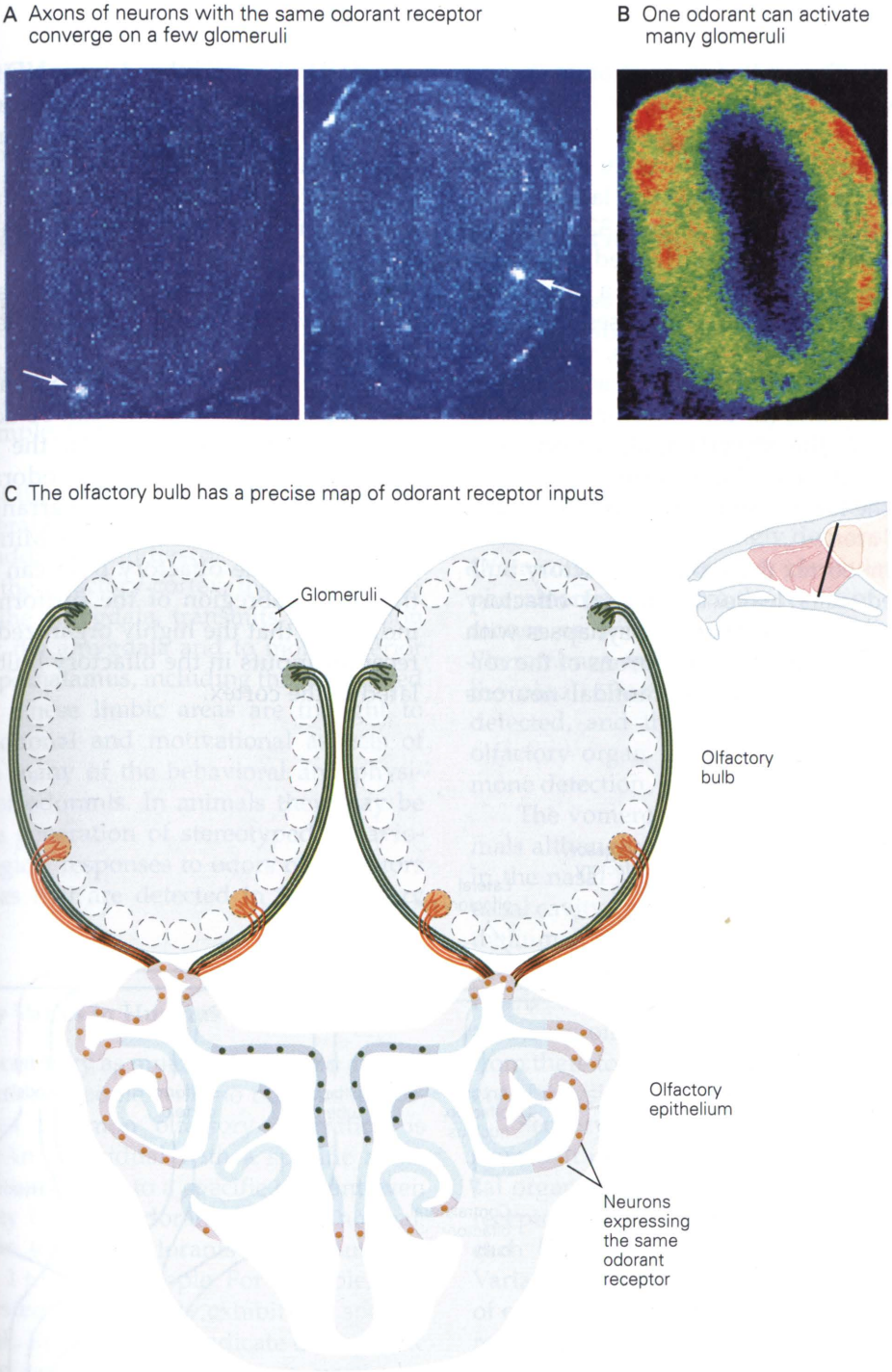


Figure 32–7 Odor responses in the olfactory bulb.

A. The axons from neurons in one epithelial zone with the same odorant receptor type usually converge to two glomeruli, one on each side of the olfactory bulb. Here a probe specific for one odorant receptor gene labeled a glomerulus on the medial side (**left**) and lateral side (**right**) of a mouse olfactory bulb. The probe hybridized to receptor messenger RNAs present in sensory axons in these coronal sections. (Adapted from Ressler, Sullivan, and Buck 1994.)

B. This section of a rat olfactory bulb shows the uptake of radiolabeled 2-deoxglucose at multiple foci (**red**) following exposure of the animal to the odorant methyl benzoate. The labeled foci correspond to numerous glomeruli at different locations in the olfactory bulb. (Reproduced, with permission, from Johnson, Farahbod, and Leon 2005.)

C. The olfactory bulb has a precise map of odorant receptor inputs because each glomerulus is dedicated to only one type of receptor. The maps in the two olfactory bulbs are bilaterally symmetrical and are nearly identical across individuals. The maps on the medial and lateral sides of each bulb are similar, but slightly displaced along the dorsal-ventral and anterior-posterior axes.

The Olfactory Bulb Transmits Information to the Olfactory Cortex

The axons of the mitral and tufted relay neurons of the olfactory bulb project through the lateral olfactory tract to the olfactory cortex (Figure 32–8 and see Figure 32–1). The olfactory cortex, defined roughly as that portion of the cortex that receives a direct projection from the olfactory bulb, comprises five main areas: (1) the anterior olfactory nucleus, which connects the two olfactory bulbs through a portion of the anterior commissure; (2) the anterior and posterior cortical nuclei of the amygdala; (3) the olfactory tubercle; (4) part of the entorhinal cortex; and (5) the piriform cortex, the largest and considered the major olfactory cortical area.

In the piriform cortex the axons of olfactory bulb mitral and tufted cells leave the lateral olfactory tract to form excitatory glutamatergic synapses with pyramidal neurons, the projection neurons of the cortex. Signal transmission by the pyramidal neurons appears to be modulated by inhibitory inputs from local GABA-ergic interneurons as well as by excitatory inputs from neighboring pyramidal neurons and the piriform cortex of the other hemisphere. The piriform cortex also receives centrifugal inputs from modulatory brain areas, suggesting that its activity may be adjusted according to behavioral state. Finally, the olfactory cortex projects to the olfactory bulb, providing yet another possible means of signal modulation.

As with the olfactory bulb relay neurons, individual pyramidal neurons can be activated by more than one odorant. However, the pyramidal neurons activated by a particular odorant are scattered across the piriform cortex, an arrangement different from that of the olfactory bulb. Mitral cells in different parts of the olfactory bulb can project axons to the same subregion of the piriform cortex, further indicating that the highly organized map of odorant receptor inputs in the olfactory bulb is not recapitulated in the cortex.

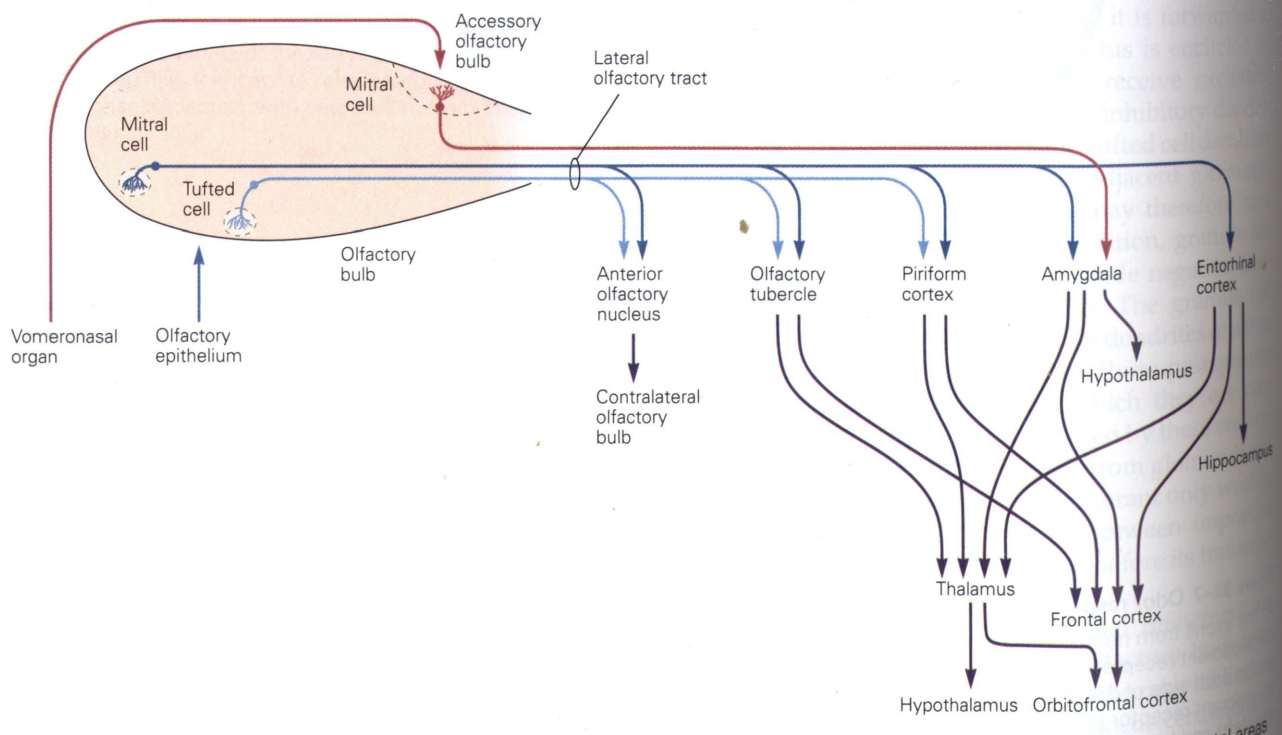


Figure 32–8 The olfactory cortex. The axons of mitral and tufted relay neurons of the olfactory bulb project through the lateral olfactory tract to the olfactory cortex. The olfactory cortex consists of a number of distinct areas, the largest of which is the piriform cortex. From these areas olfactory information is transmitted directly to other brain areas as well as indirectly via the thalamus. Targets include frontal and orbitofrontal areas of the neocortex, which are thought to be important for odor discrimination, and the amygdala and hypothalamus, which may be involved in emotional and physiological responses to odors. Mitral cells in the accessory olfactory bulb project to specific areas of the amygdala that transmit signals to the hypothalamus.

Output from the Olfactory Cortex Reaches Higher Cortical and Limbic Areas

Pyramidal neurons in the olfactory cortex transmit information indirectly to the orbitofrontal cortex through the thalamus and directly to the frontal cortex. These pathways to higher cortical areas are thought to be important in odor discrimination. In fact, people with lesions of the orbitofrontal cortex are unable to discriminate odors. Interestingly, recordings in the orbitofrontal cortex suggest that some individual neurons in that area receive multimodal input and can respond, for example, to the smell, sight, and taste of a banana.

Most areas of the olfactory cortex also relay information to the lateral hypothalamus, an area important in appetite. In addition, studies of rodents indicate that one part of the olfactory cortex, the anterior cortical nucleus of the amygdala, transmits information to other areas of the amygdala and to more anterior regions of the hypothalamus, including those involved in reproduction. These limbic areas are thought to mediate the emotional and motivational aspects of smell as well as many of the behavioral and physiological effects of odorants. In animals they may be important in the generation of stereotyped behavioral and physiological responses to odors of predators or to pheromones that are detected in the olfactory epithelium.

Olfactory Acuity Varies in Humans

Olfactory acuity can vary as much as 1,000-fold among humans, even among people with no obvious abnormality. The most common olfactory aberration is *specific anosmia*. An individual with a specific anosmia has lowered sensitivity to a specific odorant even though sensitivity to other odorants appears normal. Specific anosmias to some odorants are common, a few occurring in 1 to 20% of people. For example, 12% of individuals tested in one study exhibited a specific anosmia for musk. Recent studies indicate that specific anosmias can be caused by mutations in particular odorant receptors.

Far rarer abnormalities of olfaction, such as *general anosmia* (complete lack of olfactory sensation) or *hyposmia* (diminished sense of smell), are often transient and can derive from respiratory infections. Chronic anosmia or hyposmia can result from damage to the olfactory epithelium caused by infections; from particular diseases, such as Parkinson disease; or from head trauma that severs the olfactory nerves passing through holes in the cribriform plate, which then become blocked by scar tissue. Olfactory hallucinations of repugnant smells (*cacosmia*) can occur as a consequence of epileptic seizures.

Odors Elicit Characteristic Innate Behaviors

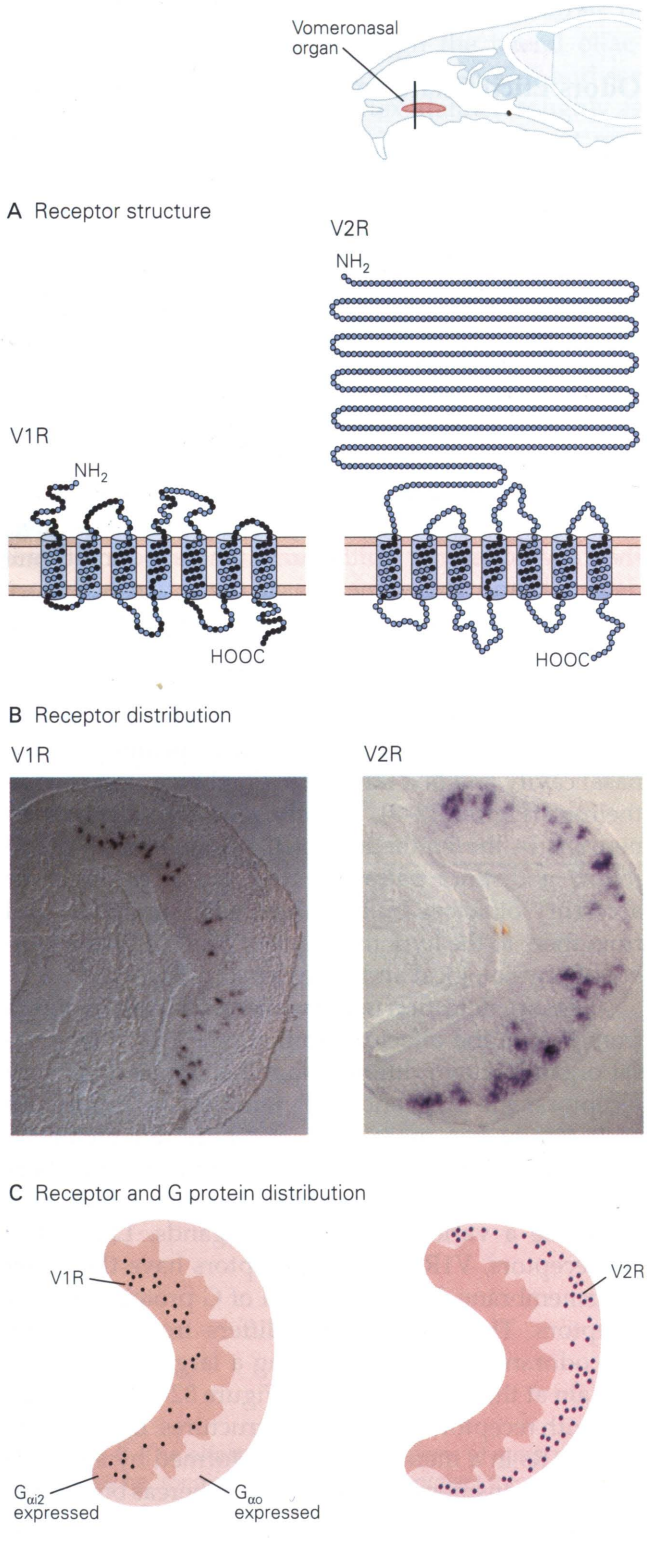
Pheromones Are Detected in Two Olfactory Structures

In many animals the olfactory system detects not only odors but also pheromones, chemicals that are released from animals and influence the behavior or physiology of members of the same species. Pheromones play important roles in a variety of mammals, although they have not been compellingly demonstrated in humans. Often contained in urine or glandular secretions, some pheromones modulate the levels of reproductive hormones or stimulate sexual behavior or aggression. Pheromones are detected by two separate structures: the nasal olfactory epithelium, where odorants are detected, and the vomeronasal organ, an accessory olfactory organ thought to be specialized for pheromone detection.

The vomeronasal organ is present in many mammals although not in humans. It is a tubular structure in the nasal septum that has a duct opening into the nasal cavity and one inner wall lined by a sensory epithelium (Figure 32–9). Signals generated by sensory neurons in the epithelium of the vomeronasal organ follow a distinct pathway. They travel through the accessory olfactory bulb to the medial amygdala and from there to the hypothalamus, which controls a variety of physiological and behavioral responses.

Sensory detection in the vomeronasal organ differs from that in the olfactory epithelium. The vomeronasal organ has two different families of chemosensory receptors, the V1R and V2R families. In the mouse each family has more than one hundred members. Variation in amino acid sequence between members of each receptor family suggests that each family may recognize a variety of different ligands. Like odorant receptors, V1R and V2R receptors have the seven transmembrane domains typical of G protein-coupled receptors. The V2R receptor differs from both V1R and odorant receptors in having a large extracellular domain at the N-terminal end (Figure 32–9A). By analogy with receptors with similar structures, ligands may bind V1Rs in a membrane pocket formed by a combination of transmembrane domains, whereas binding of V2Rs may occur in the large extracellular domain.

The V1R and V2R families are each localized in one of two zones in the vomeronasal organ that express



different G proteins (Figure 32–9B and C). The *V1R* and *V2R* genes are each expressed in a small percentage of neurons scattered throughout one zone, an arrangement similar to that of odorant receptors in the olfactory epithelium. Similar to the main olfactory bulb, the vomeronasal neurons with the same receptor type project to the same glomeruli in the accessory olfactory bulb, although the glomeruli for each receptor type are more numerous and their distribution less stereotyped than in the main olfactory bulb.

Invertebrate Olfactory Systems Can Be Used to Study Odor Coding and Behavior

Because invertebrates have simple nervous systems and often respond to olfactory stimuli with stereotyped behaviors, they are useful for understanding the relationship between the neural representation of odor and behavior.

Certain features of chemosensory systems are highly conserved in evolution. First, all metazoan animals can detect a variety of organic molecules using specialized chemosensory neurons with cilia or microvilli that contact the external environment. Second, the initial events of odor detection are mediated by families of transmembrane receptors with specific expression patterns in peripheral sensory neurons. Other features of the olfactory system differ between species, reflecting selection pressures and evolutionary histories of the animals.

The Anatomy of the Insect Olfactory System Resembles That of Vertebrates

The primary sensory organs of insects are the antennae and appendages known as maxillary palps near the mouth (Figure 32–10A). Whereas mammals have

Figure 32–9 Candidate pheromone receptors in the vomeronasal organ.

A. The V1R and V2R families of receptors are expressed in the vomeronasal organ. In the mouse each family has more than 100 members, which vary in protein sequence. Members of both families have the seven transmembrane domains of G protein-coupled receptors, but V2R receptors also have a large extracellular domain at the N-terminal end that may be the site of ligand binding.

B. Sections through the vomeronasal organ show individual V1R and V2R probes hybridized to subsets of neurons in two distinct zones. (Micrographs reproduced, with permission, from Dulac and Axel 1995 and from Matsunami and Buck 1997.)

C. The two zones express high levels of different G proteins, $G_{\alpha i2}$ and $G_{\alpha o}$.

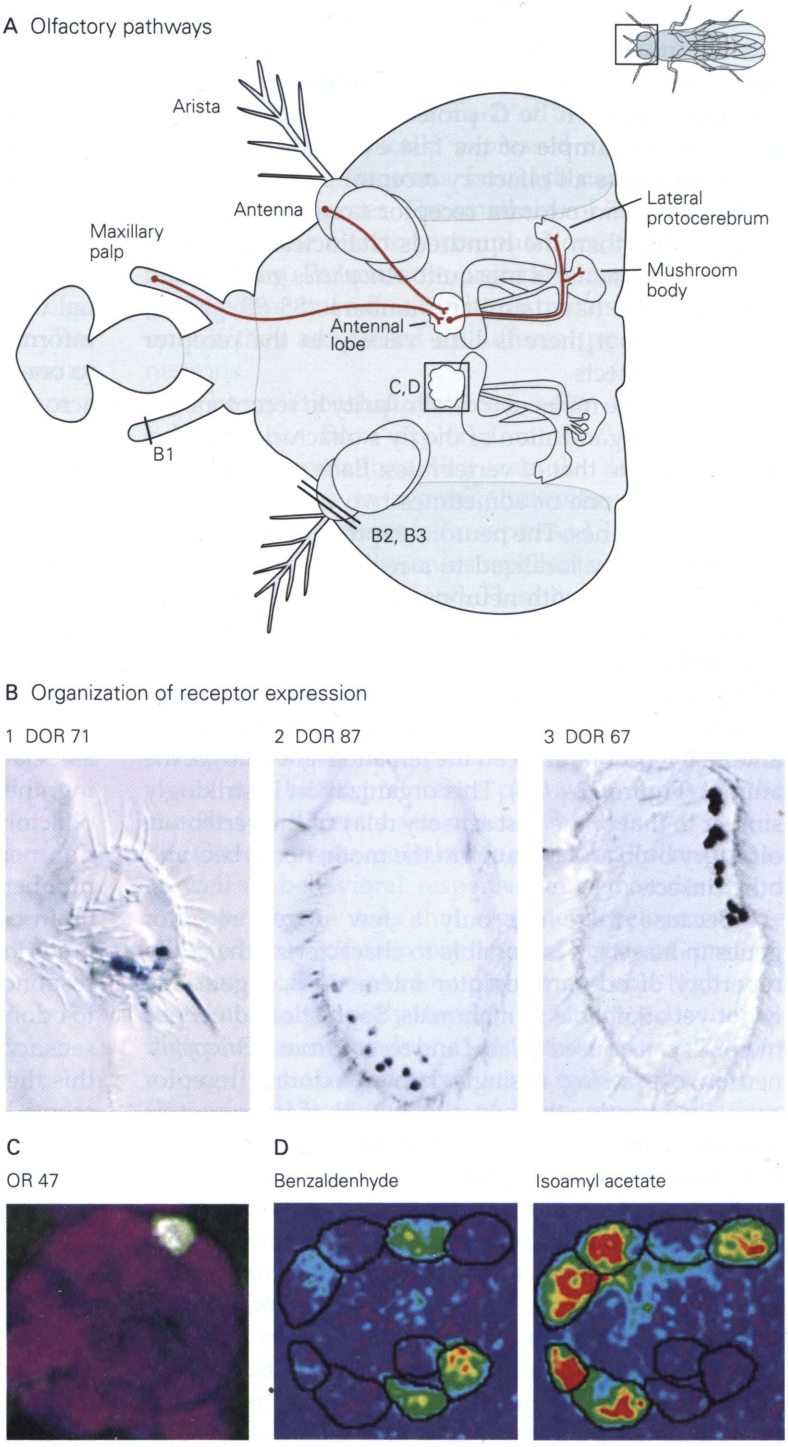


Figure 32–10 Olfactory pathways from the antenna to the brain in *Drosophila*.

A. Olfactory neurons with cell bodies and dendrites in the antenna and maxillary palp project axons to the antennal lobe. Projection neurons in the antennal lobe then project to two regions of the fly brain, the mushroom body and lateral protocerebrum. (Reproduced, with permission, from Takaki Komiyama and Liqun Luo.)

B. The neurons that express one type of olfactory receptor gene, detected by RNA in situ hybridization, are scattered in the maxillary palp (1) or antenna (2, 3).

C. All neurons that express the olfactory receptor gene *OR47* converge on a glomerulus in the antennal lobe. (Reproduced, with permission, from Vosshall et al. 1999 and from Vosshall, Wong, and Axel 2000.)

D. Each odorant elicits a physiological response from a subset of glomeruli in the antennal lobe. Two-photon calcium imaging was used to detect odor-evoked signals. (Reproduced, with permission, from Wang et al. 2003.)

millions of olfactory neurons, insects have a much smaller number. There are approximately 2,600 olfactory neurons in the simple fruit fly *Drosophila* and approximately 60,000 in a complex insect, the honeybee.

The insect odorant receptors were discovered by finding multigene receptor families in the *Drosophila* genome, and these genes have now been examined in other insect genomes as well. Remarkably, they have little similarity to mammalian odorant receptors save

for the presence of many transmembrane domains. Indeed, insect receptors appear to have an independent evolutionary origin from mammalian receptors, and may not even be G protein-coupled receptors—an extreme example of the fast evolutionary change observed across all olfactory receptor systems. In *Drosophila* the main odorant receptor family has only 60 genes rather than the hundreds characteristic of vertebrates. The malaria mosquito *Anopheles gambiae* and the honeybee have similar numbers (85–95 genes), suggesting that there is little variety in the receptor families of insects.

Despite the molecular dissimilarity in receptors, the anatomical organization of the fly's olfactory system is quite similar to that of vertebrates. Each olfactory neuron expresses one or sometimes two functional odorant receptor genes. The neurons expressing a particular gene are loosely localized to a region of the antenna, but interspersed with neurons expressing other genes (Figure 32–10B). This scattered distribution is not the case at the next level of organization, the antennal lobe. Axons from sensory neurons that express one type of receptor converge on two invariant glomeruli in the antennal lobe, one each on the left and right sides of the animal (Figure 32–10C). This organization is strikingly similar to that of the first sensory relay in the vertebrate olfactory bulb and is found in the moth, honeybee, and other insects.

Because there are only a few dozen receptor genes in insects, it is possible to characterize the entire repertory of odorant-receptor interactions, a goal that is not yet attainable in mammals. Sophisticated genetic methods can be used to label and record from a *Drosophila* neuron expressing a single known odorant receptor gene. By repeating this experiment with many receptors and odors, the receptive fields of the odorant receptors have been defined, and shown to be quite diverse.

In insects individual odorant receptors can detect large numbers of odorants, including odorants with very different chemical structures. This broad recognition of odorants by "generalist" receptors is necessary if only a small number of receptors is available to detect all biologically significant odorants. A single insect receptor protein that detects many odors can be stimulated by some odors and inhibited by others, often with distinct temporal patterns. A subset of insect odorant receptors is more selective in its recognition, and conveys information about pheromones or other unusual odors like carbon dioxide. Thus the coding potential of each olfactory neuron can be broad or narrow, and arises from a combination of stimulatory and inhibitory signals delivered to its receptors.

Information from the olfactory neurons is relayed to the first processing station, the antennal lobe (Figure 32–10A). Sensory neurons expressing the same odorant receptor converge onto a small number of projection neurons in one glomerulus of the antennal lobe. Because *Drosophila* glomeruli are stereotyped in position and have one type of odorant receptor input, the transformation of information across the synapse can be described. Convergence leads to a great increase in signal-to-noise ratios of olfactory signals, so projection neurons are much more sensitive to odor than individual olfactory neurons. Within the antennal lobe most information from an individual olfactory neuron goes to one glomerulus, but information is also distributed across the entire antennal lobe and processed by excitatory and inhibitory interneurons that connect many glomeruli. Excitatory interneurons distribute signals to projection neurons at distal locations, and inhibitory interneurons feed back onto the olfactory sensory neurons to dampen their input.

The projection neurons from the antennal lobe extend to higher brain centers called mushroom bodies and lateral protocerebrum (Figure 32–10A). These structures may represent insect equivalents of the olfactory cortex. The mushroom bodies are sites of olfactory associative learning and multimodal associative learning; the lateral protocerebrum is important for innate olfactory avoidance responses. At this stage projection neurons form complex connections with a large number of downstream neurons. Neurons in higher brain centers in *Drosophila* have the potential to integrate information from many receptors. Because they respond to only a small number of odors, their tuning to odors appears to be far more specific than that of the sensory neurons or antennal projection neurons. Even this higher-order pattern in the lateral protocerebrum seems highly reproducible from fly to fly, suggesting that a detailed higher-order map of insect odor representation can be defined.

Olfactory Cues Elicit Stereotyped Behaviors and Physiological Responses in the Nematode

The nematode roundworm *Caenorhabditis elegans* has one of the simplest nervous systems in the animal kingdom, with only 302 neurons in the entire animal. Of these, 32 are ciliated chemosensory neurons. Because *C. elegans* has strong behavioral responses to a wide variety of chemicals it has been a useful animal for relating olfactory signals to behavior. Each chemosensory neuron detects a specific set of chemicals and activation of the neuron is required for the behavioral responses to those substances. The neuron for a particular response, such as attraction to a specific odor, occurs in the same position in all individuals.

The molecular mechanisms of olfaction in *C. elegans* were elucidated through genetic screens for anosmic worm mutants. The G protein-coupled receptor for the volatile odorant diacetyl emerged from these screens (Figure 32–11). This receptor is one of approximately 1,700 predicted G protein-coupled chemoreceptor genes in *C. elegans*, the largest number of chemoreceptors among known genomes. Other kinds of chemosensory receptors are also present; for example, *C. elegans* senses external oxygen levels indirectly by detecting soluble guanylate cyclases that bind directly to oxygen. With so many chemoreceptors, nematodes are able to recognize a large variety of odors with great sensitivity. Downstream of the receptors some chemosensory neurons use G proteins to regulate cyclic guanosine 3′–5′ monophosphate (cGMP) and a cGMP-gated channel, a signal transduction pathway like that of vertebrate photoreceptors. Other chemosensory neurons signal through a transient receptor potential vanilloid (TRPV) channel, like vertebrate nociceptive neurons.

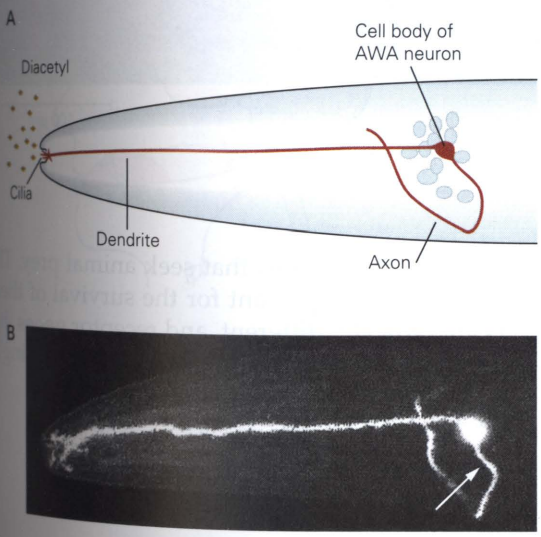


Figure 32–11 The receptor for diacetyl is expressed in a specific chemosensory neuron in the nematode worm *C. elegans*.

A. A lateral view of the worm's anterior end shows the cell body and processes of the AWA chemosensory neuron. The dendritic process terminates in cilia that are exposed to environmental chemicals. The neuron detects the volatile chemical diacetyl; animals with a mutation in the *odr-10* gene are unable to sense diacetyl.

B. The *odr-10* gene product, marked with a fusion to a fluorescent reporter protein, is seen only in the AWA neuron, whose axon is marked with an arrow. (Reproduced, with permission, from Sarafi-Reinach and Sengupta 2000.)

The "one neuron, one receptor" principle observed in vertebrates and insects does not operate in nematodes as the number of neurons is much smaller than the number of receptors. Each of the many chemoreceptor genes is typically expressed in only one pair of chemosensory neurons, but each neuron expresses many receptor genes. The small size of its nervous system limits the olfactory computations that *C. elegans* can perform. For example, a single neuron responds to many odors, but odors can be distinguished efficiently only if they are sensed by different primary sensory neurons.

The relationship between odor detection and behavior has been explored in *C. elegans* through genetic manipulations. For example, diacetyl is normally attractive to worms, but when the diacetyl receptor is experimentally expressed in an olfactory neuron that normally senses repellents, the animals are instead repelled by diacetyl. This observation indicates that specific sensory neurons encode the hardwired behavioral responses of attraction or repulsion, and that a "labeled line" connects specific odors to specific behaviors. Similar ideas have emerged from genetic manipulations of taste systems in mice and flies, where sweet and bitter preference pathways appear to be encoded by different sets of sensory cells.

Olfactory cues are linked to physiological responses as well as behavioral responses in nematodes. Food and pheromone cues that regulate development are detected by specific sensory neurons through G protein-coupled receptors. At low pheromone and high food levels animals rapidly develop to adulthood, whereas high pheromone levels and scarce food drive entry into a long-lived arrested larval stage called a *dauer larva* (Figure 32–12). Activation of these sensory neurons ultimately regulates the activity of an insulin signaling pathway that controls physiology and growth, as well as life span, of the nematode. It is an open question whether the chemosensory systems and physiological systems of other animals are as entangled as they are in nematodes.

Strategies for Olfaction Have Evolved Rapidly

Why have independent families of odorant receptors evolved in mammals, nematodes, and insects? And why have the families changed so rapidly compared to genes involved in other important biological processes? The answer lies in a fundamental difference between olfaction and other senses such as vision, touch, and hearing.

Most senses are designed to detect physical entities with reliable physical properties: photons, pressure, or sound waves. By contrast, olfactory systems are designed

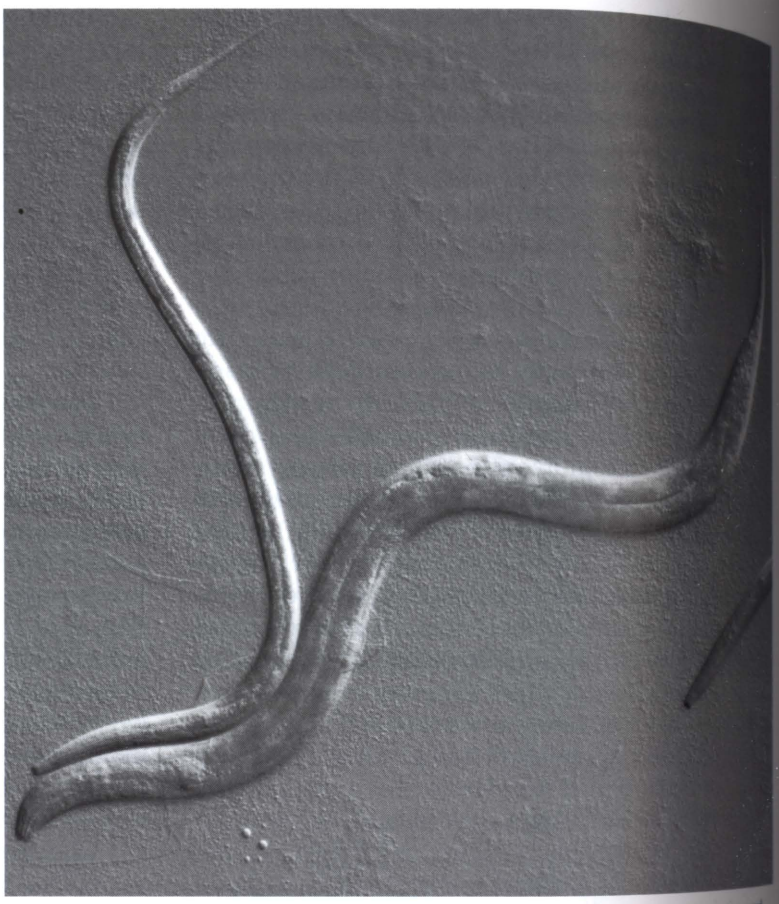


Figure 32–12 Chemosensory cues regulate the development of *C. elegans*. When exposed to different chemosensory cues, two larvae of the same age adopt distinct fates. At the left is a dauer larva, a small, slender animal that forms under stressful conditions of low food and high animal density. The dauer larva is a nonfeeding, nonreproductive, stress-resistant form. At the right is a fourth-larval-stage animal in a rich environment favoring reproductive growth. (Reproduced, with permission, from Manuel Zimmer.)

to detect organic molecules that are infinitely variable and do not fit into a simple continuum of properties. Moreover, the organic molecules that are detected are produced by other living organisms, which evolve far more rapidly than the world of light, pressure, and sound.

An ancient olfactory system was present in the common ancestors of all animals that exist today. That ancestor lived in the ocean, where it gave rise to different lineages for mammals, insects, and nematodes. Those three phyla of animals came onto land hundreds of millions of years after the phyla diverged. Each phylum independently modified its olfactory system to detect airborne odors, leading to diversification of the receptors.

A consideration of the natural history of dipteran and hymenopteran insects, which have evolved in the last 200 million years, helps explain the rapid diversification of the odorant receptors. These insects include honeybees that pollinate flowers, fruit flies that feed on rotting fruit, flesh flies that arrive within minutes of death, and mosquitoes that seek animal prey. The odorants that are important for the survival of these insects are radically different, and receptor genes that are tuned to those odorants have evolved accordingly.

The Gustatory System Controls the Sense of Taste

Taste Has Five Submodalities or Qualities

The primary function of the gustatory system is nutritional. Humans and other mammals can distinguish five different taste qualities: sweet, bitter, salty, sour, and umami, the taste associated with amino acids. Taste chemicals (tastants) perceived as sweet are associated with food high in caloric content, while those sensed as umami are indicative of protein.

Consistent with the nutritional importance of carbohydrates and proteins, both sweet and umami

tastants elicit pleasurable sensations in humans and are attractants for animals. In contrast, bitter tastants, which are often found in poisonous plants, elicit an aversive response that is innate in animals as well as human infants and likely prevents the ingestion of toxic substances.

Taste is often thought to be synonymous with flavor. However, taste refers strictly to the five qualities encoded in the gustatory system, whereas flavor, with its rich and varied qualities, actually stems from a combination of inputs from the gustatory, olfactory, and somatosensory systems.

Taste Detection Occurs in Taste Buds

In the gustatory system sensory signals generated in the mouth are relayed through the brain stem and thalamus to the gustatory cortex (Figure 32–13). Tastants are detected by taste receptor cells that are clustered in taste buds. Although the majority of taste buds in humans are located on the tongue, some can also be found on the palate, pharynx, epiglottis, and upper third of the esophagus.

Taste buds on the tongue occur in structures called papillae, of which there are three types based on morphology and location. *Fungiform papillae*, located on the anterior two-thirds of the tongue, are peg-like structures that are topped with taste buds. Both the *foliate papillae*, situated on the posterior edge of the tongue, and the *circumvallate papillae*, of which there are only a few in the posterior area of the tongue, are structures surrounded by grooves lined with taste buds (Figure 32–14A). Each fungiform papilla contains one to five taste buds, while each circumvallate or foliate papilla contains hundreds.

The taste bud is a garlic-shaped structure embedded in the epithelium. A small opening at the epithelial

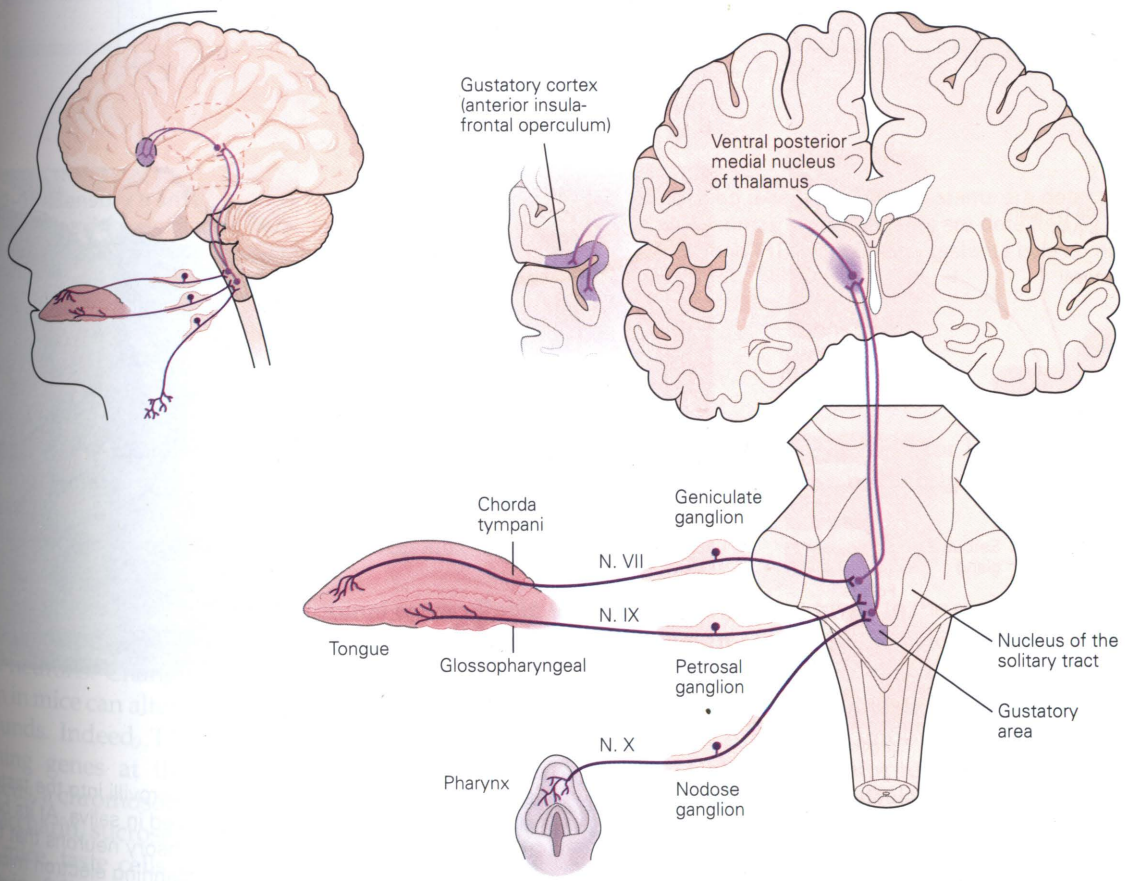


Figure 32–13 The gustatory system. Tastants are detected in taste buds in the oral cavity. Taste buds on the tongue are innervated by the peripheral fibers of gustatory sensory neurons, which travel in the glossopharyngeal and chorda tympani nerves and terminate in the nucleus of the solitary tract in the brain stem. From there taste information is relayed through the thalamus to the gustatory cortex as well as to the hypothalamus.

surface, the taste pore, is the point of contact with tastants (Figure 32–14B). Each taste bud contains approximately 100 taste receptor cells (taste cells), elongated cells that stretch from the taste pore to the basal area of the bud. The taste bud also contains other elongated cells that are thought to serve a supporting function, as well as a small number of round cells at the base, which are thought to serve as stem cells. Taste cells are short-lived and appear to be continually replaced from the stem cell population.

Each taste cell extends microvilli into the taste pore, allowing the cell to contact chemicals dissolved in saliva at the epithelial surface. At its basal end the taste cell contacts the afferent fibers of gustatory sensory neurons, whose cell bodies reside in specific sensory ganglia (Figures 32–13 and 32–14). Although taste cells are nonneural, their contacts with the gustatory sensory neurons have the morphological characteristics of chemical synapses, including clustered presynaptic vesicles. Taste cells also resemble neurons in that they are electrically excitable; they have voltage-gated Na^+, K^+, and Ca^{2+} channels and are capable of generating action potentials.

Each Taste Is Detected by a Distinct Sensory Transduction Mechanism and Distinct Population of Taste Cells

Each of the five taste qualities involves a different sensory transduction mechanism in the microvilli of taste cells. There are, however, two general types. Bitter, sweet, and umami tastants interact with G protein-coupled receptors, whereas salty and sour tastants appear to involve specific ion channels (Figure 32–15). These interactions depolarize the taste cell, leading to the generation of action potentials in the afferent gustatory fibers.

Sweet Taste

Compounds that humans perceive as sweet include sugars, artificial sweeteners such as saccharin and

Figure 32–14 Taste buds are clustered in papillae on the tongue.

A. The three types of papillae—circumvallate, foliate, and fungiform—differ in morphology and location on the tongue and are differentially innervated by the chorda tympani and glossopharyngeal nerves.

B. Each taste bud contains 50 to 150 elongated taste receptor cells, as well as supporting cells and a small population of basal stem cells. The taste cell extends microvilli into the taste pore, allowing it to detect tastants dissolved in saliva. At its basal end the taste cell contacts gustatory sensory neurons that transmit stimulus signals to the brain. The scanning electron micrograph shows a taste bud in a foliate papilla in a rabbit. (Reproduced, with permission, from Royer and Kinnamon 1991.)

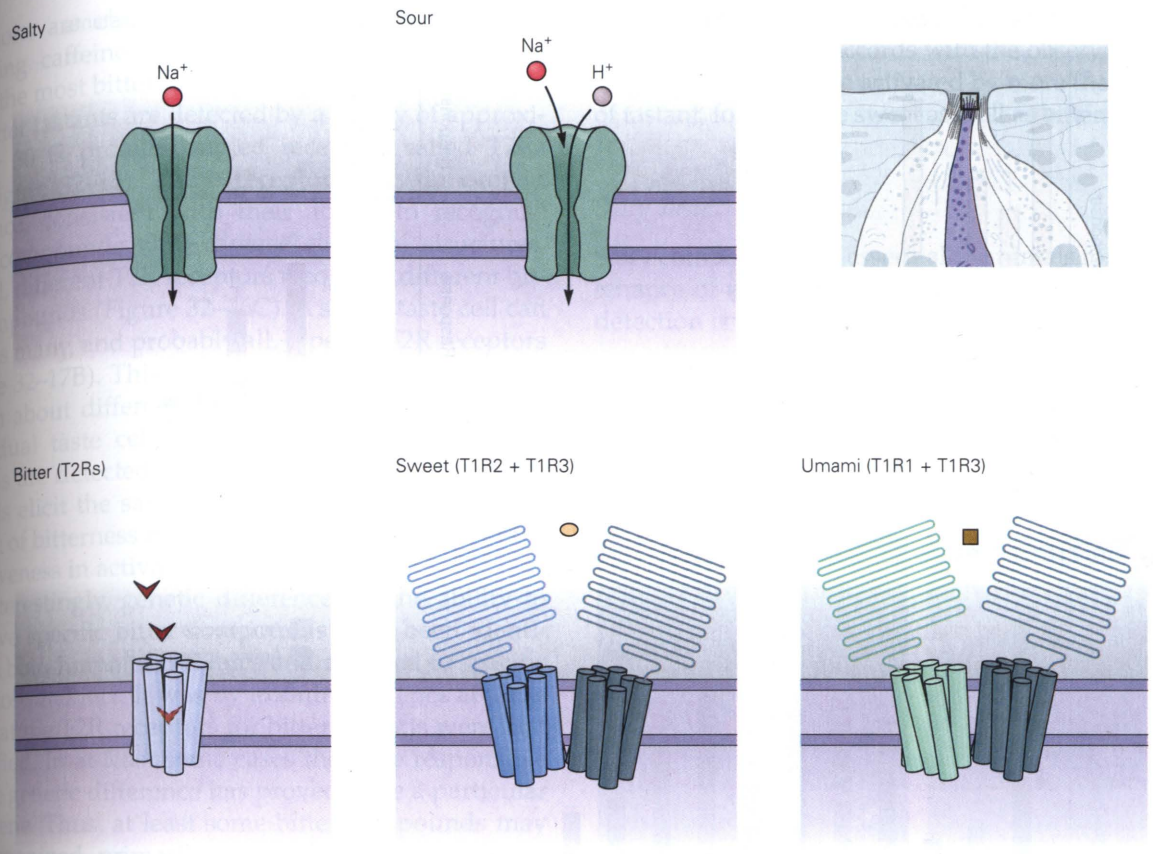


Figure 32–15 Sensory transduction in taste cells. Different taste qualities involve different detection mechanisms in the microvilli at the apical taste pore of taste cells (see Figure 32–14B). Salty and sour tastants activate ion channels, whereas tastants perceived as bitter, sweet, or umami activate G protein-coupled receptors. Bitter tastants are detected by T2R receptors, whereas sweet tastants are detected by a combination of T1R2 and T1R3 and umami tastants by a combination of T1R1 and T1R3.

aspartame, a few proteins such as monellin and thaumatin, and some D-amino acids. All of these sweet-tasting compounds are detected by a complex of two related G protein-coupled receptors, T1R2 and T1R3 (Figure 32–16).

T1R receptors have a large N-terminal extracellular domain (Figure 32–15) like the V2R receptors of vomeronasal neurons. Changing a single amino acid in this domain in mice can alter an animal's sensitivity to sweet compounds. Indeed, T1R3 was initially discovered by examining genes at the mouse saccharin preference (Sac) locus, a chromosomal region that governs sensitivity to saccharin, sucrose, and other sweet compounds.

In mice, taste cells with T1R2 receptors are found mostly in foliate and circumvallate papillae; almost invariably those cells also possess T1R3 receptors (Figure 32–17A). Gene knockout experiments in mice indicate that the T1R2/T1R3 complex mediates the detection of all sweet compounds except for high concentrations of sugars, which can also be detected by T1R3 alone.

Umami Taste

Umami is the name given to the savory taste of monosodium glutamate, an amino acid widely used as a flavor enhancer. It is believed that the pleasurable sensation associated with umami taste encourages the ingestion of proteins and is thus important to nutrition.

The taste cell receptor responsible for umami taste is a complex of two related G protein-coupled receptors: T1R1 and T1R3 (Figure 32–15). In both humans and mice the T1R1/T1R3 complex can interact with all L-amino acids (Figure 32–16B), but in humans it is preferentially activated by glutamate. Purine nucleotides, such as inosine 5′-monophosphate (IMP), are often added to monosodium glutamate to enhance its

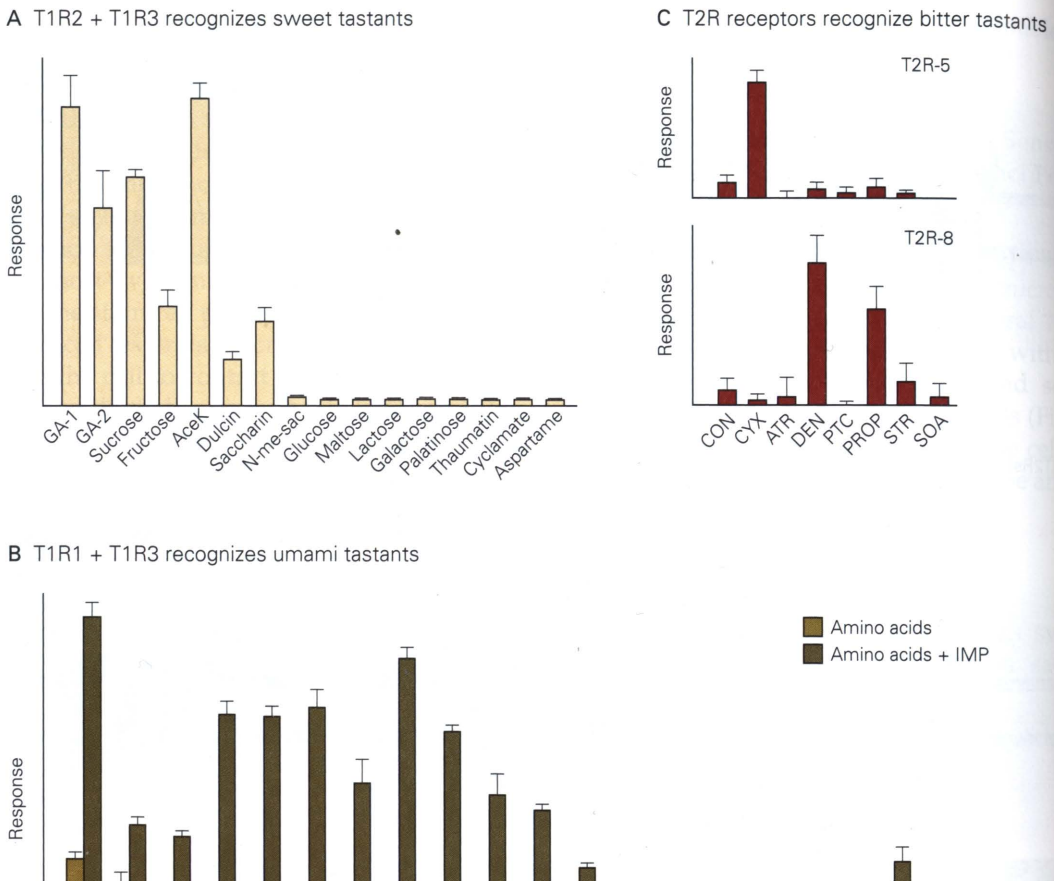


Figure 32–16 Tastants recognized by T1R and T2R receptors. A calcium-sensitive dye was used to test whether T1R and T2R receptors expressed in a tissue culture cell line could detect tastants.

A. Cells expressing both rat T1R2 and rat T1R3 responded to a number of sweet compounds. (Reproduced, with permission, from Nelson et al. 2001.)

B. Cells expressing mouse T1R1 and mouse T1R3 responded to numerous L-amino acids (umami taste). Responses were potentiated by inosine monophosphate (IMP). (Reproduced, with permission, from Nelson et al. 2002.)

C. Cells expressing different T2R receptors responded selectively to different bitter compounds. Cells expressing mouse T2R5 responded most vigorously to cycloheximide (CYX), whereas cells expressing mouse T2R8 responded preferentially to denatonium (DEN) and 6-n-propyl-2-thiouracil (PROP). (ATR, atropine; **CON**, control; **PTC**, phenyl thiocarbamide; **SOA**, sucrose octaacetate; **STR**, strychnine.) (Reproduced, with permission, from Chandrashekar et al. 2000.)

pleasurable umami taste. Interestingly, in vitro studies show that IMP potentiates the responsiveness of T1R1/T1R3 to L-amino acids, suggesting that IMP acts on the receptor itself (Figure 32–16B).

Taste cells with both T1R1 and T1R3 are concentrated in fungiform papillae (Figure 32–17A). Studies in mice in which individual T1R genes have been deleted indicate that the T1R1/T1R3 complex is solely responsible for umami taste.

Bitter Taste

Bitter taste is thought to have evolved as a means of preventing ingestion of toxic molecules. Bitter taste

sensations are elicited by a variety of compounds, including caffeine, nicotine, alkaloids, and denatonium, the most bitter-tasting compound known.

Bitter tastants are detected by a family of approximately 30 G protein-coupled receptors called T2Rs (see Figure 32–15). These receptors vary in protein sequence, consistent with their ability to recognize bitter compounds with diverse chemical structures. Indeed, different T2R receptors recognize different bitter compounds (Figure 32–16C). A single taste cell can express many, and probably all, types of T2R receptors (Figure 32–17B). This arrangement implies that information about different bitter tastants is integrated in individual taste cells. Because different bitter compounds are detected by the same cells, all these compounds elicit the same perceptual quality: bitter. The degree of bitterness might be caused by a compound's effectiveness in activating bitter taste cells.

Interestingly, genetic differences in the ability to perceive specific bitter compounds have been identified in both humans and mice and mapped to specific chromosomal loci. It was by examining genes at these loci that the T2R receptors for bitter tastants were first identified. In at least some cases the gene responsible for the genetic difference has proved to be a particular T2R gene. Thus, at least some bitter compounds may be recognized primarily or perhaps exclusively by only one of the 30 or so T2R receptor types.

In mice taste cells expressing T2R receptors are found in both foliate and circumvallate papillae (Figure 32-17C). Taste cells express either T2R or T1R receptors, but a single taste bud can contain taste cells of both types. Such mixing of cells accords with the observation that a single taste bud can be activated by more than one class of tastant, for example sweet as well as bitter.

Salty Taste

Salty compounds are essential to animals for the maintenance of electrolyte balance. It is thought that their detection is mediated by specific ion channels, but the

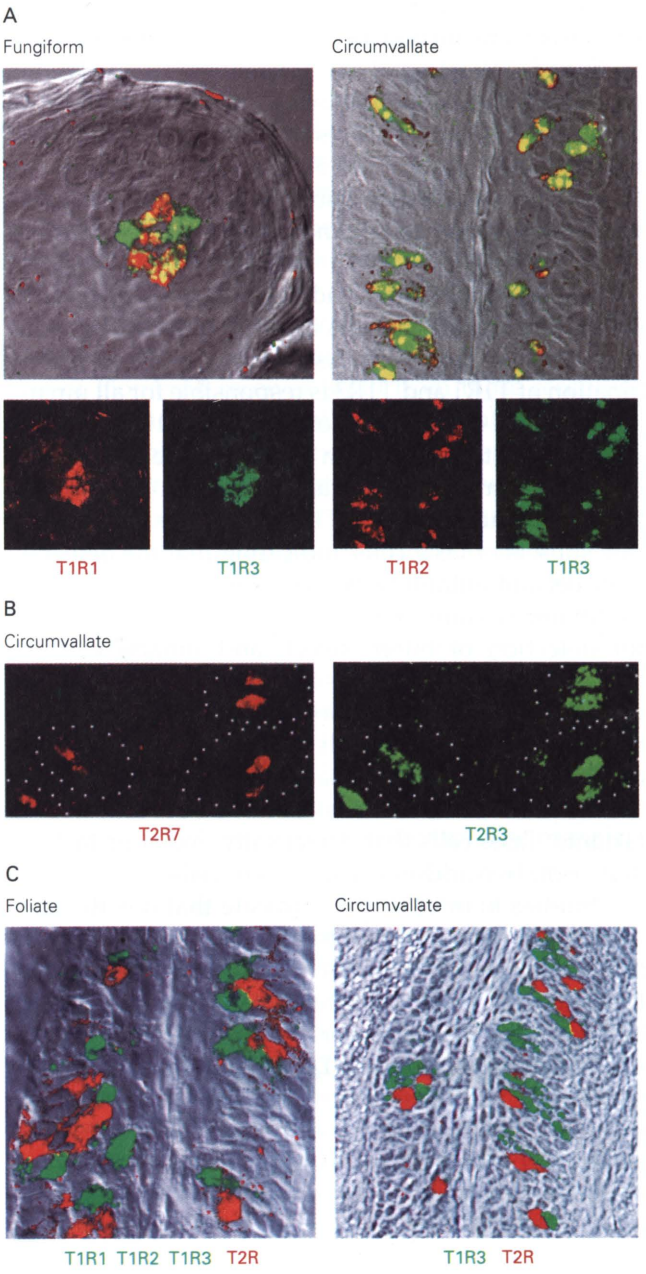


Figure 32–17 Expression of T1R and T2R receptors on the tongue. Sections of mouse or rat tongue were hybridized to probes that label T1R or T2R mRNAs to detect their sites of expression in taste cells.

A. T1R3 is expressed in taste cells of all three types of papillae. However, T1R1 is found mostly in fungiform papillae, whereas T1R2 is located predominantly in circumvallate (and foliate) papillae. Overlap between sites of expression appears as yellow cells in the panels at the top. The T1R1-T1R3 umami receptor is more frequently found in fungiform papillae, whereas the T1R2-T1R3 sweet receptor is more frequently found in circumvallate and foliate papillae. (Reproduced, with permission, from Nelson et al. 2001.)

B. A taste cell that detects bitter tastants can express several different T2R receptors. Here probes for T2R3 and T2R7 labeled the same taste cells in circumvallate papillae. (Reproduced, with permission, from Adler et al. 2000.)

C. T1R and T2R receptors are expressed in different taste cells. Taste cells labeled by a T1R3 probe or mixed T1R probes (green) did not overlap with cells labeled by a mixture of T2R probes (red). (Reproduced, with permission, from Nelson et al. 2001.)

underlying mechanisms are not yet known (see Figure 32–15). Detection of sodium chloride (NaCl), for example, might result from a diffusion of Na^+ ions down an electrochemical gradient through Na^+ channels on taste cell microvilli, or it might involve ion channels that are opened by Na^+ ions.

Sour Taste

Sour taste is associated with acidic food or drink. As with bitter compounds, animals are innately averse to sour substances, prompting the suggestion that the adaptive advantage of sour taste is avoidance of spoiled foods.

The molecular mechanisms underlying sour stimulus transduction in the taste cell have not been identified. Detection of sour tastants may involve ion channels that are opened by H^+ ions or that allow an influx of those ions that results in a depolarization of the taste cell (Figure 32–15). However, as with salty taste, the proteins responsible for sour taste transduction have not yet been defined.

Molecular-genetic studies indicate that bitter, sweet, and umami tastants are each detected by a distinct subset of taste cells. As already discussed, a combination of T1R1 and T1R3 is responsible for all umami taste, while a combination of T1R2 and T1R3 is needed for all sweet taste detection except for the detection of high concentrations of sugars, which can be mediated by T1R3 alone. T1R1 and T1R2 are expressed by separate subsets of taste cells, indicating that the detection of sweet and umami tastants is segregated.

In mice a transduction protein (PLCb2) is required for detection of bitter, sweet, and umami tastants. When this protein is expressed only in cells with bitter receptors, the cells are responsive to bitter compounds but not to sweet compounds or amino acids. This result confirms that taste cells that detect bitter compounds are distinct from those that detect sweet and umami tastants. Taste cells that detect salty and sour tastants may form two additional subsets of cells.

Studies in mice further indicate that it is the taste cells rather than the receptors that determine the animal's response to a tastant. The human bitter receptor T2R16 recognizes a bitter tastant that mice cannot detect. When this receptor was expressed in mouse taste cells that express the T1R2/T1R3 sweet complex, the human T2R ligand elicited an attractive response; when it was expressed in mouse cells that express T2R bitter receptors, the same ligand instead caused aversion. These findings suggest that innate responses of mice to sweet and bitter compounds result from specific gustatory pathways (labeled lines) that link the activation of different subsets of taste cells to different behavioral outcomes.

Sensory Neurons Carry Taste Information from the Taste Buds to the Brain

Each taste cell is innervated at its base by the peripheral branches of the axons of primary sensory neurons (Figure 32–14). Each sensory fiber branches many times, innervating several taste cells within numerous taste buds. The release of neurotransmitter from taste cells onto the sensory fibers induces action potentials in the fibers and the transmission of signals to the sensory cell body.

The cell bodies of gustatory sensory neurons lie in the geniculate, petrosal, and nodose ganglia. The peripheral branches of gustatory sensory neurons in these three ganglia travel in cranial nerves VII, IX, and X (Figure 32–13).

The central branches of axons of the gustatory sensory neurons enter the medulla, where they terminate on neurons in the gustatory area of the nucleus of the solitary tract (Figure 32–13). In most mammals neurons in this nucleus transmit signals to the parabrachial nucleus of the pons, which in turn sends gustatory information to the ventroposterior medial nucleus of the thalamus. In primates, however, these neurons transmit gustatory information directly to the taste area of the thalamus.

Taste Information Is Transmitted from the Thalamus to the Gustatory Cortex

From the thalamus taste information is transmitted to the gustatory cortex, a region of the cerebral cortex located along the border between the anterior insula and the frontal operculum (Figure 32–13). The gustatory cortex is believed to mediate the conscious perception and discrimination of taste stimuli. The taste area of the thalamus also transmits information both directly and indirectly to the hypothalamus, a structure that controls feeding behavior and autonomic responses.

Recordings made from neurons in the gustatory cortex indicate that some neurons respond to different classes of tastants, whereas others respond to only one, such as bitter or sweet. It might be that neurons responsive to more than one class of tastants encode information about blends whereas those in gustatory cortex or other areas that respond to single taste categories are involved in innate responses, such as attraction to sweet tastants or aversion to bitter tastants.

Perception of Flavor Depends on Gustatory, Olfactory, and Somatosensory Inputs

Much of what we think of as the flavor of foods derives from information provided by the olfactory system. Volatile molecules released from foods or beverages in the mouth are pumped into the back of the nasal cavity by the tongue, cheek, and throat movements that accompany chewing and swallowing. Although the olfactory epithelium of the nose clearly makes a major contribution to sensations of flavor, such sensations are localized in the mouth rather than in the nose.

The somatosensory system is thought to be involved in this localization of flavors. The coincidence between somatosensory stimulation of the tongue and the retronasal passage of odorants into the nose is assumed to cause odorants to be perceived as flavors in the mouth. Sensations of flavor also frequently have a somatosensory component that includes the texture of food as well as sensations evoked by spicy and minty foods and by carbonation.

Insect Taste Organs Are Distributed Widely on the Body

Like vertebrates, insects have specialized organs for taste. Some of the taste neurons occur in internal mouth parts. Others lie near the mouth on the proboscis, or are scattered on the leg, wing, and oviposition organs.

The gustatory receptors of *Drosophila* are membrane-spanning receptors that are very distantly related to the odorant receptors of the fly. The fly has approximately 60 gustatory receptor genes, a surprisingly large number considering it has approximately 60 olfactory receptor genes. Members of the gustatory receptor gene family are expressed in all of the different kinds of taste organs. Some occur in particular cell types, whereas others are present in many parts of the body.

As in vertebrates, in flies numerous taste receptor genes appear to be expressed in a single neuron. Sweet-sensing and bitter-sensing neurons in the labial palp mediate food acceptance or rejection, respectively. Other neurons have distinct functions. For example, neurons in the male leg express gustatory receptors that are involved in recognizing females during courtship.

An Overall View

The senses of smell and taste allow us to evaluate volatile molecules in our environment and both volatile and nonvolatile components of foodstuffs. Humans can perceive a vast number of volatile chemicals as having a distinct odor and distinguish odorants with nearly identical structures.

The basic design and functional capacities of olfactory systems are highly conserved across vertebrate species and to some extent in invertebrates. In addition to providing a means of distinguishing between appropriate and potentially harmful substances prior to ingestion, the sense of smell also plays an important role in predator-prey relationships as well as the regulation of social relationships critical to reproduction and the rearing of offspring.

Odorant detection in the nose is mediated by hundreds of different odorant receptors, each expressed by a subset of neurons. Different combinations of odorant receptors detect specific odorants and encode their identities. In the olfactory epithelium neurons with the same receptor are randomly distributed throughout one spatial zone. In the olfactory bulb the axons of neurons with the same type of receptor all converge in a few glomeruli, such that each glomerulus and its associated relay neurons are dedicated to one type of odorant receptor. Thus in the nose the code for an odorant is dispersed across an ensemble of neurons, each expressing one receptor component of the odorant's code, whereas in the olfactory bulb a specific combination of glomeruli receives input from those receptors, an arrangement that is similar in different individuals.

In the olfactory cortex neurons responsive to a given odorant are distributed broadly, but the underlying organization of sensory inputs is unknown. The olfactory cortex transmits information to a variety of other brain areas, including higher cortical areas involved in perception and the hypothalamus, which controls appetite and other basic drives.

Pheromones that elicit innate behavioral or physiological responses are detected in the nasal olfactory epithelium as well as in the vomeronasal organ, an olfactory structure present in most mammals, although not in humans. The vomeronasal organ has two different families of chemosensory receptors. The organization of inputs from these receptors resembles that seen for odorant receptors, but vomeronasal signals travel through a separate neural pathway that targets the hypothalamus but not cortical brain areas.

Humans can distinguish five taste qualities: bitter, salty, sweet, sour, and umami. Salty and sour taste detection is thought to involve specific ion channels, whereas the other three taste qualities derive from G protein-coupled receptors. Three classes of receptors are expressed by separate subsets of taste cells, but a single taste cell expresses many or all of the T2R bitter receptors. Studies in transgenic mice indicate that

innate attraction to sweet tastants and aversion to bitter tastants involve hardwired neural pathways that link different subsets of taste cells on the tongue to different behavioral outcomes. The perception of blends of tastants may involve the gustatory cortex, where some neurons can respond to more than one class of tastants.

Studies of flies and worms have revealed a striking similarity to mammals in the strategies used to detect and distinguish chemicals in the external environment. In the fruit fly *Drosophila* and the nematode *C. elegans*, large families of receptors mediate the detection of environmental chemicals. Although the neural circuits that carry inputs from these receptors differ from those in mammals, they have certain features in common with mammals, suggesting that studies of these relatively simple organisms could provide insight into mechanisms underlying chemosensation in vertebrates as well as invertebrates. Because odors and tastes often elicit innate behaviors in these organisms, they also provide a means of exploring neural circuits that mediate instinctive behaviors.

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Symbols

C Capacitance (measured in farads).

c_m Capacitance per unit length of membrane cylinder.

C_m Membrane capacitance: either total input capacitance of a cell (measured in units of F) or capacitance of a unit area of membrane ($F \cdot cm^{-2}$), depending on context.

E Equilibrium (or Nernst) potential of an ion species, e.g., E_{Na}, or reversal potential for current through an ion channel.

F Faraday's constant (9.65×10^4 coulombs per mole).

G Conductance (measured in siemens).

g Conductance of a population of ion channels to one or more ion species, e.g., g_{Na}.

g_l Resting (leakage) conductance; total conductance of a population of resting (leakage) ion channels.

I Current (measured in amperes). The flow of charge per unit time, $\Delta Q/\Delta t$. Ohm's law, $I = V \cdot G$, states that current flowing through a conductor (G) is directly proportional to the potential difference (V) imposed across it.

I_c Capacitive current; the current that changes the charge distribution on the lipid bilayer.

I_i Ionic current; the resistive current that flows through ion channels.

I_l Leakage current; the current flowing through a population of resting ion channels.

I_m Total current crossing the cell membrane.

i Current flowing through a single ion channel.

Q Excess positive or negative charge on each side of a capacitor (measured in coulombs).

R Gas constant ($1.99\ cal \cdot {}^\circ K^{-1} \cdot mol^{-1}$).

R Resistance (measured in ohms). The reciprocal of conductance, $1/G$.

R_{in} Total input resistance of a cell.

R_m Specific resistance of a unit area of membrane (measured in $\Omega \cdot cm^2$).

r Resistance of a single ion channel.

r_a Axial resistance of the cytoplasmic core of an axon, per unit length (measured in Ω/cm).

r_m Membrane resistance, per unit length (measured in $\Omega \cdot cm$).

V_m Membrane potential, $V_m = Q/C_{in}$ (measured in volts).

V_r Resting membrane potential.

V_t Threshold of membrane potential above which the neuron generates an action potential.

V_{in} Potential on the inside of the cell membrane.

V_{out} Potential on the outside of the cell membrane.

Z Valence.

γ Conductance of a single ion channel, e.g., γ_{Na}

λ Cell membrane length constant (typical values 0.1–1.0 mm). $\lambda = \sqrt{r_m/r_a}$

τ Cell membrane time constant; the product of resistance and capacitance of the membrane (typical values 1–20 ms). $\tau = R_m \cdot C_m$

Units of Measurement

A Ampere, measure of electric current (SI base unit). One ampere of current represents the movement of 1 coulomb of charge per second.

Å Ångström, measure of length (10^{-10} m, non-SI unit).

C Coulomb, measure of quantity of electricity, electric charge (expressed in SI base units $s \cdot A$).

F Farad, measure of capacitance (expressed in SI base units $m^2 \cdot kg^{-1} \cdot s^4 \cdot A^2$).

Hz Hertz, measure of frequency (expressed in s^{-1}).

M Molar measure of concentration of a solution (moles of solute per liter of solution).

mol Mole, measure of amount of substance (SI base unit).

mol wt Molecular weight.

S Siemens, measure of conductance (expressed in SI base units $m^{-2} \cdot kg^{-1} \cdot s^3 \cdot A^2$).

V Volt, measure of electric potential, electromotive force (expressed in SI base units $m^2 \cdot kg \cdot s^{-3} \cdot A^{-1}$). One volt is the energy required to move 1 coulomb a distance of 1 meter against a force of 1 newton. Measurements in cells are in the range of millivolts (mV).

Ω Ohm, measure of electric resistance (expressed in SI base units $m^2 \cdot kg \cdot s^{-3} \cdot A^{-2}$).

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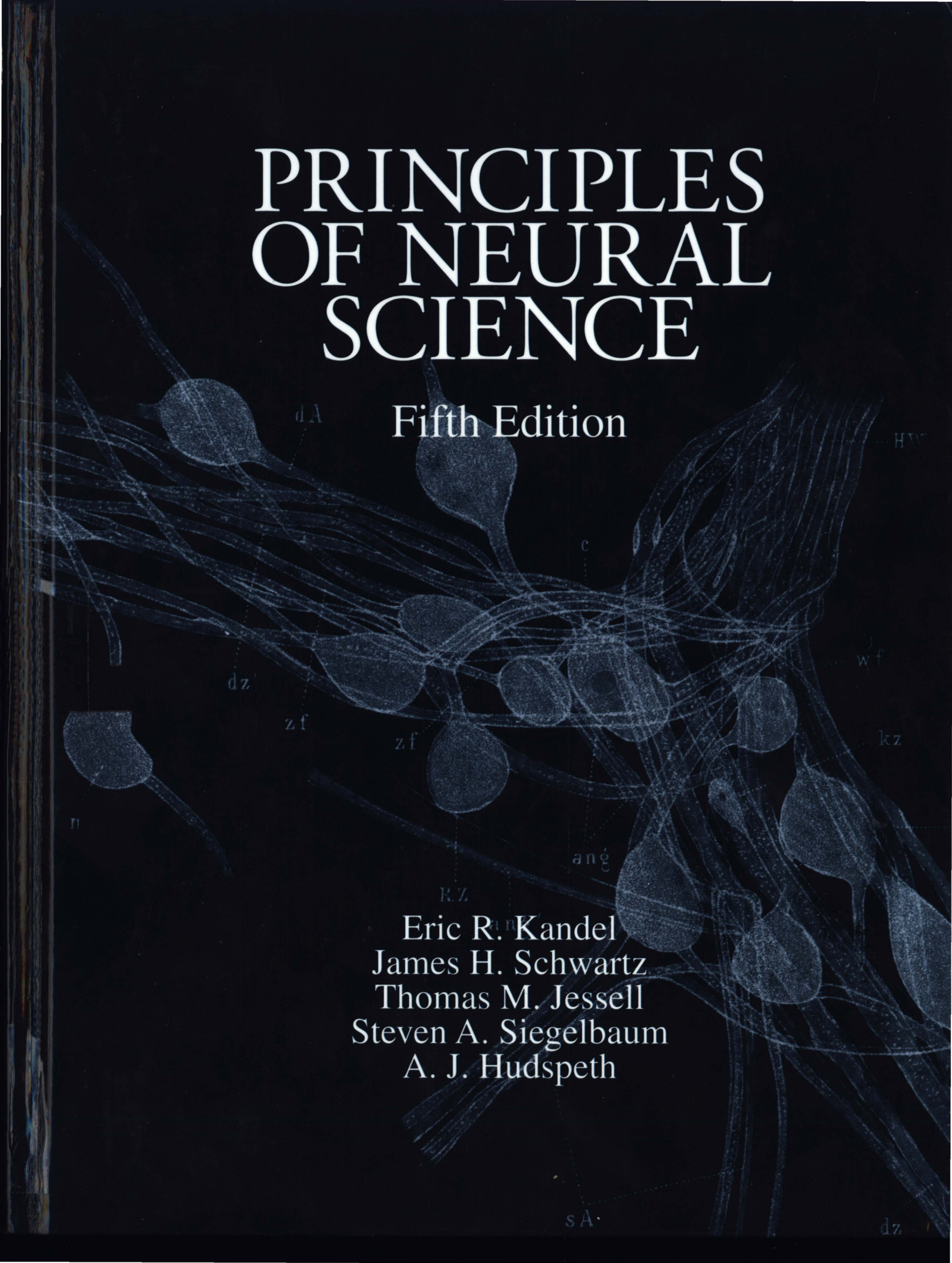

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